LONGTERM FOLLOW-UP OF ANTI-MÜLLERIAN HORMONE LEVELS IN PATIENTS WHO HAD SURGERY FOR ENDOMETRIOMA

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DECLARATION:

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights. The research contained in this dissertation has previously been submitted in article format to The College of Obstetrician and Gynaecologist for partial fulfilment of the qualification Certificate in Reproductive Medicine of the Colleges of Medicine of South Africa.

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ABSTRACT:

Introduction:

Endometriosis is highly prevalent among women of reproductive age increasing up to 50% in those presenting with infertility. Ovarian endometriosis, known as endometriomas, is found in up to 44% of women with endometriosis. Excisional surgery for endometrioma in the form of cystectomy is associated with a reduction in ovarian reserve as measured by anti-Müllerian hormone (AMH). Although there are reports of recovery of AMH levels following cystectomy, the long-term effects of this surgery on ovarian reserve is unknown.

Objective and Methods:

The primary objective is to investigate whether there is recovery of serum anti-Müllerian hormone (AMH) level in the long-term (more than 1 year) after cystectomy for endometriomas, with a secondary objective to determine the on-going pregnancy rate in the group of patients trying to conceive. We performed a longitudinal cohort study in a tertiary referral unit evaluating fifty-nine patients that underwent laparoscopic cystectomy for suspected endometrioma. We analysed data on serum-AMH levels of samples collected before or on the day of surgery, 6 months after surgery and at a mean final follow-up of 23.3 months after surgery. For our secondary outcome we determined a documented clinical pregnancy in patients that whished to conceive

Results:

The serum AMH levels declined in 92% of patients at final follow-up. A significant decline in serum AMH of -1.23ng/ml and -1.47ng/ml was detected at 6 months and final follow-up respectively. We demonstrated an on-going pregnancy rate of 38% in the groups trying to conceive.

Conclusion:

The reduction in ovarian reserve following cystectomy as measured by serum AMH does not recover in the overwhelming majority of patients. Patients need to be counselled regarding this possibility and alternative fertility sparing options should be considered in the management of endometriomas in women still wishing to conceive.

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TABLE OF CONTENTS:

CHAPTER 1: Pathophysiology of the endometrioma

1.1 Introduction:

The prevalence of endometriosis among women of reproductive age ranges between 6-10% increasing up to 50% in those presenting with infertility.(1) Endometriomas are found in up to 44% of women with endometriosis, with which it shares its pathogenesis.(2) Although there are numerous hypotheses for the pathogenesis of endometriosis, it is now widely accepted that there are three distinct phenotypes of the disease in the pelvis.

1.2 Phenotypes:

The first phenotype of endometriosis is so-called peritoneal endometriosis, these typical superficial lesions are characterised by proliferative glands with either columnar or pseudo-stratified epithelium. In the early stages of endometriosis these appear as red lesions that regrows constantly with cyclical hormone fluctuation inducing local inflammation. This chronic inflammation induces scar formation resulting in enclosure of the implant causing accumulation of debris, and development of a typical black endometriotic lesion.(3)

Another phenotype is that of deep-infiltrating endometriosis often involving the recto-vaginal septum. These lesions are most likely not infiltrating but rather result from local metaplasia of residual Müllerian cells embryologically deposited in these areas. Lesions often involve a collection of smooth muscle fibres, glandular and stromal

endometrial tissue. Proliferation and fibrosis of these smooth-muscle fibres result in the typical nodular appearance of these lesions, which can be palpated with vaginal or rectal examination.(3)

The third phenotype, and the main focus of this dissertation, is that of ovarian endometriosis mostly presenting in cystic form and commonly referred to as an ovarian endometrioma. These cysts invariably contain homogenous dark-brown fluid of medium consistency. This fluid represents accumulated menstrual debris, and have lead to the often used term of “chocolate cyst” to describe this particular phenotype.(4)

1.3 Pathogenesis of endometrioma:

The exact pathogenesis of these endometriotic ovarian cysts is still being debated. One of the most commonly cited theories for the development of an endometrioma is that it results from an endometriotic focus on the surface of the ovary. The associated inflammation then causes adhesion between this endometriotic focus and the peritoneal surface, most often the posterior aspect of the broad ligament.(5) This results in a confined endometriotic deposit that is sensitive to the cycling circulating hormones associated with a regular menstrual cycle. After hormonal stimulation of these deposits, and subsequent withdrawal, these active endometriotic implants shed similar to the endometrium with which it shares its histology. Accumulation of this menstrual debris in the occluded space between the ovarian and peritoneal surfaces results in invagination of the ovarian cortex at this point.(6) Over time this leads to development of an extra-ovarian pseudocyst. This implies that these cysts

does not have a true cyst wall, but that what appears macroscopically to be a cyst wall, is in actual fact invaginated stretched out ovarian cortex.(4)

An alternative mechanism for the development of an endometrioma relies on the metaplasia theory, similar to that of the development of other forms of endometriosis. A layer of mesothelium covers the ovarian surface and has been shown on histological investigation to invaginate and result in inclusions in the ovary. This mesothelial layer is pluripotent and metaplasia of its cells can result in the development of intra-ovarian glandular epithelium and stroma akin to endometriosis. Similar to the previously discussed mechanism, continuous hormonal stimulation and shedding of endometrium, result in accumulation of debris and subsequent cyst formation in these inclusion cysts.(7)

A final pathogenic mechanism for the formation of ovarian endometrioma involves the transformation of functional ovarian cysts into endometrioma. The most common functional cyst implicated in the process is the cystic corpus luteum. It is proposed that the inflammation and possible adhesions associated with active peritoneal endometriotic implants predetermine the site of ovulation and subsequent corpus luteal formation. Potent fibrinolytic agents produced by endometriotic implants could predispose to haemorrhagic corpus luteum formation followed by secondary colonisation by ectopic endometrial cells.(8)

1.4 Conclusion:

Regardless of the exact process of its pathogenesis, it is clear from all available literature that the ovarian endometrioma is not a typical ovarian cyst with a well-defined capsule, but rather a pseudocyst with a capsule that is in fact thinly stretched out ovarian cortex.(9) This fact in the pathogenesis of an endometrioma has serious implications for its management as any attempt at removal could potentially damage or remove some of the residual ovarian tissue with a resultant decrease in functional ovarian reserve.

CHAPTER 2: Ovarian reserve

2.1 Introduction:

Ovarian reserve is a term used to describe the size of the remaining follicular pool in the ovary. A declining follicular pool and oocyte quality is a hallmark of natural female ageing, but can also be accelerated by autoimmune disease, endometriosis and surgery to the ovary.(10)

2.2 Ovarian reserve tests:

Testing for ovarian reserve aims to quantify or estimate the remaining follicular pool in the ovary. Various biological, biochemical, biophysical and even histological tests have been described with the aim to quantify the ovarian reserve.(10)

Advancing age is associated with a declining follicular pool, and widely considered a biological marker for ovarian reserve. Although age is considered the most import factor with regard to fertility potential, it is not suitable for quantifying the effect of surgery on ovarian reserve.(10)

Antral follicle count (AFC) is a sonar parameter denoting the number of antral follicles as measured with trans-vaginal ultrasound in the early follicular phase. Antral follicles are regarded as the follicles with a mean diameter, measured in two perpendicular planes, measuring between 2-6mm. AFC is most often used in an assisted reproductive setting to predict poor or normal response to ovarian

hyperstimulation.(10) AFC has also been used for the quantification of ovarian reserve in patients with endometriomas or following ovarian surgery for endometriomas. Studies do however raise the question of the accuracy of AFC in the case of an operated ovary to accurately predict the ovarian reserve.(11) This query along with the logistical issue of timing the AFC ultrasound in the early the follicular phase precludes it from being the ideal marker for estimating the effect of surgery on ovarian reserve in a research setting.

Density of follicles can be determined histologically from an ovarian biopsy specimen obtained at the time of laparoscopy. This follicular density in conjunction with the ovarian volume could thus be use estimate the ovarian reserve. The accuracy of an ovarian biopsy to quantity the density of follicles is however questionable as follicles are not necessarily distributed equally across the ovary and the biopsy might thus not be representative of the true density.(10)

Basal follicle stimulation hormone (FSH), produced in the anterior lobe of the pituitary gland, can be use as a surrogate marker for ovarian reserve. Inhibin B is a glycoprotein hormone secreted by pre-antral follicles. This hormone provides negative feedback to the pituitary thus controlling the release of FSH. As the pool of pre-antral follicles decrease the amount of negative feedback provided by inhibin B decreases, resulting in a subsequent rise in FSH levels.(12) Although no exact cut-off points exist, high FSH levels in the early follicular phase of the cycle can be used to estimate the ovarian reserve and response to stimulation and thus identify a diminished ovarian reserve.(12)

Other dynamic measures of ovarian reserve such as early follicular estradiol levels or the clomiphene citrate challenge test as demonstrated significant inter-cycle variability and are thus not reliable markers for routinely measuring ovarian reserve.(12)

2.3 Anti-Müllerian Hormone:

Anti-Müllerian hormone (AMH) has been extensively studied as a marker of ovarian reserve. AMH is a glycoprotein produced by the granulosa cells in the pre-antral and small antral follicles, and therefore provides quantification of the residual follicular pool in the ovary.(10,12) AMH correlates well with the clinical antral follicle count. This hormone is not usually influenced by follicular development and thus displays no inter-cycle variability. AMH can be measured in the serum at any time during the menstrual cycle making it a more objective and easy method of measuring the ovarian reserve.(10,13) The introduction of measurement of serum levels for AMH by enzyme linked immunosorbent assay (ELISA) was initially plagued by technical issues. The initial essays displayed complement interference and required modified protocols and extensive manual execution, resulting in a lack of standardisation and reproducibility of results.(14,15) The recent introduction of standardised automated assays has however overcome the initial issues with ELISA AMH testing. These automated assay are now producing comparable results and have been externally validated.(15)

Currently the main application of AMH is in predicting the ovarian response to gonadotropin stimulation during assisted reproductive treatment. This not only allows

for the prediction of a poor response but also identifies the patient with a high AMH that is at risk of developing ovarian hyperstimulation syndrome.(14) Due to the fact that serial determination of AMH can determine the loss of ovarian function, it is increasingly being employed to quantify the effect of endometriosis and associated ovarian surgery on ovarian reserve.(14,16)

2.4 Conclusion:

Although various methods and modalities for measuring ovarian reserve exit, issues of reproducibility and intra- and inter-cycle variability plague most of them. AMH however, notwithstanding its limitations, provides the most objective and reproducible measure of quantifying the remaining follicle pool and an ideal tool for studying the effects of surgical intervention on ovarian reserve.

CHAPTER 3: Surgical management of endometrioma

3.1 Introduction:

It has been a long held view that medical management on its own does not satisfactorily and definitively treat ovarian endometriomas, and most often do not lead to complete resolution of the cyst, but at most a reduction size. Subsequently the surgical management of endometriomas is often favoured and has been regarded as the standard of care in these cases.(2)

3.2 Aspiration of the endometrioma:

Ultrasound-guided percutaneous drainage, either trans-abdominally or trans-vaginally, could be regarded as the least invasive surgical modality in the management of endometrioma. The biggest drawback to this technique is the high recurrence rate reported by several investigators.(2)

More recently some groups have employed ethanol as a sclerosing agent at the time of endometrioma aspiration. They report favourable outcomes in endometriomas up to the size of 10 cm and propose this as an ovarian sparing approach to the management of these cysts. There is however limited data on the effect of this technique on ovarian reserve and fertility potential or pregnancy outcome following its use.(17) Although promising, the risk of complications such as infection and

adhesions and the inability to obtain adequate histology at the time of aspiration coupled with a high recurrence rate have led to aspiration not being regarded as a first line strategy in the management of endometrioma. One exception to this statement could be when considering the management of an endometrioma in the context of assisted reproductive treatment involving a patient that as already underwent multiple previous surgeries. Additional surgical intervention could further delay her infertility treatment and compromise an already diminished ovarian reserve. In these cases consideration can be give to conservative treatment in the form of aspiration of the endometrioma prior to starting ovarian stimulation with the aim of doing in-vitro fertilisation (IVF).(2)

3.3 Cystectomy for endometrioma:

Cystectomy in the context of surgery for an endometrioma refers to the excision of the apparent cyst wall performed either at open surgery or more recently and preferably at laparoscopic surgery. The current best level of evidence point to this excisional approach being superior to less radical intervention such as drainage or ablation with regard to recurrence of the endometrioma and pain as well as a reported improvement in spontaneous pregnancy rates following cystectomy.(18)

Cystectomy involves the opening and draining of the endometrioma at the time of laparoscopy. This is followed by careful identification of the cyst wall, aided by laparoscopic magnification, and meticulously stripping it off the ovarian parenchyma, utilising two atraumatic laparoscopic forceps with traction and counter-traction developing and following a cleavage plane.(19) Given the accepted pathophysiology

of an endometrioma, as already discussed in the opening chapter, there is often a lack of a clearly defined surgical plane. This is firstly due to pseudo-cystic nature of the endometrioma itself, not possessing an anatomically defined cyst wall, and secondly due to associated endometriosis induced fibrosis that surrounds the cyst.(20) Excisional surgery thus has a high risk of inadvertently removing ovarian parenchyma especially in regions with dense fibrosis where it can be extremely difficult to find a good cleavage plane.(20) This potential removal of healthy and viable ovarian tissue has been studied by evaluating the histological specimens of cystectomies performed for endometriomas for the presence of ovarian stroma and follicles. Presence of ovarian tissue could be confirmed in 40 to 100% of histology samples following cystectomies.(19–21) Although this loss of ovarian tissue could contribute to the loss of ovarian function, the effects of excision or stripping of the cyst could be exaggerated by the concomitant vascular compromise in the remaining ovarian tissue. This would most likely be caused by injudicious use of bipolar coagulation or any other energy source on the remaining raw ovarian surface to achieve haemostasis resulting in a destruction of functional ovarian tissue and reduced ovarian reserve.(21,22)

3.4 Cystectomy and ovarian reserve:

It is clear from the literature reviewed thus far that excisional surgery for endometrioma in the form of cystectomy could compromise the ovarian reserve. Somigliana et al systematically reviewed 11 articles investigating the effect of excisional management of ovarian endometriomas utilising the stripping technique on ovarian reserve as measured by AMH. Nine of the 11 studies demonstrated a

statistically significant decline in AMH following surgery.(23) AMH decline has been reported up to six month after the index surgery. The magnitude of the decline in AMH level was also more pronounced in cases where bilateral cystectomy was performed for endometrioma, or where the cysts being removed were larger than 5 cm.(16,24)

The concept that ovarian reserve can recover after cystectomy has been discussed in the literature before.(25) Previous studies reporting on serial changes in AMH values following ovarian cystectomy for endometrioma have suggested that levels could recover at one year after surgery. Vignali et al. evaluated 22 patients and did not demonstrate any difference between AMH levels pre-operatively and at 12 months after cystectomy.(26) Another study evaluating the recovery of ovarian reserve after cystectomy reported an increase in AMH level in 51% of patients at 1 year.(27)

3.5 Conclusion:

Although the mere presence of ovarian endometriosis could influence the function of the immediate adjacent ovarian parenchyme, the pathogenesis of an ovarian endometrioma dictates that excisional surgery invariable should have a negative effect on the surrounding viable ovarian tissue. The disease itself or surgical technique as well as the size and presence of bilateral cysts could influence the degree of the reduction in ovarian reserve. Recovery of this resultant insult to the ovarian reserve has however not been adequately studied.

CHAPTER 4: A Cohort Study: Long-term effect on ovarian reserve of surgery for endometrioma

4.1 Introduction:

Although cystectomy is regarded as the preferred management of endometrioma (18), it is currently being questioned because of the possibility that it could remove ovarian tissue due to the absence of a clearly defined cyst capsule.(28) This along with the resultant vascular compromise could result in a decrease in ovarian reserve.(22) Although this decline in ovarian reserve as measured by AMH has been well proven in the short-term (23), there is a paucity of data relating to the long-term effects of ovarian cystectomy for endometrioma.

4.2 Aim:

This study aims to determine the long-term effects of ovarian surgery on ovarian reserve. It studies a cohort of patients undergoing ovarian cystectomy for endometrioma followed-up over an extended period of longer than a year with the main aim to determine the long-term impact of surgery for endometriomas on the ovarian reserve as reflected by AMH. We aimed to determine the recovery or failure to recover of serum-AMH levels at long-term follow-up, as well the reproductive outcomes in these patients.

4.3 Objectives:

The primary objective was to determine the trend in serum-AMH levels after 12 months in patients that underwent laparoscopic ovarian cystectomy for endometriomas. The secondary objective was to determine the reproductive outcome in those patients that were trying to conceive.

4.4 Materials and Methods:

The patients in this study were previously recruited as part of a prospective cohort study evaluating changes in AMH 6 months after laparoscopic cystectomy.(29) The current study presents a long-term (>12 month) follow-up of this cohort and reports a 3rd AMH value at >12 months as well as their reproductive outcomes up to the last follow-up date.

Patients were recruited before surgery and included if they had sonographic features suggestive of uni- or bilateral endometrioma. Clinical and demographic data were collected and all surgery was done laparoscopically at a tertiary referral centre. Patients were excluded if the intra-operative findings did not confirm the presence of an endometrioma in at least one of the ovaries.

Surgery was performed under general anaesthesia. A standard 4 port laparoscopic approach involved establishing a pneumoperitoneum with a Verres needle and closed primary entry at the umbilicus followed by placement of additional ports under direct vision. Surgery involved appropriate adhesiolysis and mobilisation of ovaries

from the ovarian fossae. The endometrioma was opened with monopolar energy and its content aspirated. Cystectomy was performed by gentle traction and counter-traction with two atraumatic graspers taking care of the cleavage plane and avoiding damage to ovarian cortex. At the areas where no clear plane could be identified the surface of the cyst was ablated using an argon beam coagulator. If needed, haemostasis was achieved by applying the argon beam coagulator. The rest of the procedure involved addressing any concurrent peritoneal and recto-vaginal endometriosis by ablation or excision. All specimens were sent for histologic confirmation of endometriosis.

Initial serum AMH values were determined pre-operatively or on the day of surgery and again at 6 months following the surgery. At long-term follow-up (>12 months after surgery), serum AMH was again determined. Persistence of any symptoms as well as recurrence of endometrioma was noted. Patients that had repeated cystectomy during the follow-up period were excluded in the final analysis of AMH values. The reproductive outcomes of patients after the initial surgery were also recorded.

4.5 Data management:

Data was extracted from patient files and laboratory results pertaining to the study question. Data was extracted with a custom-made data extraction tool and entered into an EXCEL spreadsheet and presented for statistical analysis.

Three AMH assays were used during the course of this study namely the AMH GenII (Beckman Coulter), Access (Beckman Coulter) and Elecsys (Roche). The majority of samples were tested using the automated Elecsys platform. All other results were converted by using the Passing-Bablock regression equations described by Nelson et al (15) before statistical analysis, to allow for accurate comparison of all values.

Data was analysed with STATA 14 (STATACorp) and WIZARD 1.9.13 (E.MILLER) data analysis software. A random effects model was used to compare values at different times. We used the Student's *t* test to compare changes in values between different groups.

4.6 Ethical approval:

Ethical approval for this study was obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences of Stellenbosch University, protocol no S17/02/027.

4.7 Results:

A total of 59 patients were recruited to undergo surgery for suspected endometrioma. At surgery 7 patients were found not to have an endometrioma and 2 patients were lost to follow-up, thus 50 patients were included for analysis at a final mean follow-up period of 23.3 months (95% CI, 20.9-25.8) after surgery. The mean age of patients was 34.4(±6.07) with the majority (68%) having a unilateral

endometrioma and 54% (n=27) also had recto-vaginal endometriosis. The baseline characteristics are represented in Table 1.

For the primary outcome evaluating the long-term effect on ovarian reserve following cystectomy, 26 patients with 3 AMH values were included. These values were measured at surgery, 6 months after surgery and at final follow-up respectively. The pre-operative, 6-month and final follow-up AMH levels were 2.60±1.76/1.56 (mean±SD/median), 1.36±0.71/1.28 and 1.13±0.82/1.02, respectively. This represents a statistically significant decline of -1.23(95%CI:-1.84 - -0.62; P<0.001) at 6 months and -1.47(95%CI:-2.08 - -0.86: P<0.001) at final follow-up. Twenty-four patients (92%) showed a decline of their AMH levels equating to an overall decline of 50.5% (95%CI:34.9-66.0) in the mean AMH levels at final follow-up.

Bilateral endometriomas were associated with a significantly greater reduction in AMH values with a mean reduction of -2.79±1.98ng/ml compared to -0.77±0.49ng/ml in patients with unilateral endometriomas (P=0.008). In those patients with a decline in AMH value at final follow-up this represents a reduction of 38.9±20.6% for unilateral and 72.2±18.5% for bilateral endometriomas respectively (P=0.033).

A large number of patients (n=34) were actively trying to conceive following the surgery, with an on-going pregnancy rate of 38% (n=13) during the follow-up period. The majority of pregnancies were conceived spontaneously (54%, n=7).

CHAPTER 5: Discussion, limitations and conclusion

5.1 Discussion:

There is growing consensus in the literature that an ovarian endometrioma is not a true cyst of the ovary but rather an invagination of the ovarian cortex by progressive accumulation of menstrual debris from active endometriotic deposits.(3,7,4) The origin of this endometriotic focus is however still debated with the two most popular theories being that of a superficial implant resulting from retrograde menstruation, as proposed by Sampson, or metaplasia occurring in the mesothelium lining of an ovarian inclusion cysts.(7) Regardless of the exact pathophysiology, the absence of a true cyst wall results in significant adherence to underlying ovarian parenchyma, with no clearly defined cleavage plane. (5)

Previous studies with variable length of follow-up after surgery have reported that ovarian reserve could potentially recover after the initial drop shortly after the surgery.(25,26) Our study is unique because of the long follow-up period of AMH levels that extends to a mean of 23.3 months (95% CI, 20.9-25.8). Over this extended period we have failed to demonstrate a recovery in AMH values at final follow-up, but rather a further decline (1.23±1.06ng/ml) compared to the values at 6 months after surgery (1.36±0.94ng/ml).

Few studies have evaluated the pregnancy rate in patients trying to conceive after cystectomy for endometriomas. Taniguchi et al. reported a cumulative pregnancy rate of 50% among 40 patients undergoing laparoscopic cystectomy for ovarian

endometrioma.(30) In our study we found an on-going pregnancy rate of 38% (13/34) among women trying to conceive after surgery. Seven of the pregnancies were spontaneous, 2 required ovulation induction and 4 resulted from in-vitro fertilisation. Previous studies have shown the preoperative AMH levels are not predictive of pregnancy rates following endometriosis surgery.(31) We demonstrated no statistical difference in pre-operative or final follow-up of AMH between patients achieving pregnancy and those who did not.

It has become clear that the traditional technique of cystectomy for the endometrioma could have a detrimental effect on ovarian reserve and reduce subsequent fertility (23,32). Other surgical approaches in the management of endometriomas might reduce the impact on ovarian reserve. Hydro-dissection with or without the addition if dilute vasopressin have been suggested to aid in identifying the correct surgical plane thus possibly reducing the risk of inadvertently removing normal ovarian tissue.(33,34) Vasopressin, as vasoconstrictor, has the added benefit of limiting the need for excessive coagulation to achieve haemostasis and in this way limits potential damage to ovarian reserve.(33,35) Another alternative would include the combined technique involving partial stripping of the cyst wall with ablation of any residual endometriotic foci at the more vascular hilar area.(36,37) Alternatively, especially in the very large endometrioma, a 3-step approach with initial laparoscopic drainage followed by GnRH suppression for 3 months and ablation of the base of the cyst at repeat laparoscopy could be used in an attempt to limit damage to the ovary.(7)

Although much controversy still exists, it seems that cystectomy for endometrioma does not improve the outcome of in vitro fertilisation cycles (IVF), and thus proceeding with ART prior to extensive surgery should be considered.(38,39) In such cases thought should be given to offering medical suppression of the endometriosis with gonadotropin releasing hormone agonists (GnRHa) followed by controlled ovarian hyperstimulation and IVF.(40) Although this may be suitable for women with an immediate desire for pregnancy, in those that would like to delay conception, ovarian stimulation with oocyte vitrification might be an option to protect their future fertility before undergoing extensive endometriosis surgery.(41) This should especially be considered in younger patients with bilateral or recurrent endometriomas.

There are however clinical scenarios where complete cystectomy could be indicated and individualisation in these cases are needed. One of the disadvantages of not performing a cystectomy is the absence of histology confirming the benign nature of the cyst.(42) The association of the histological finding of atypical endometriosis and the development of clear cell and endometrioid carcinoma of the ovary contributes to a growing view that these lesions could be regarded as premalignant.(43) The presence of enhanced mural nodularity in ovarian endometrioma have also been associated with histological findings of malignancy.(44) Recurrence of endometriomas is associated with an increased risk of developing atypical endometriosis.(45,46) Taking all of these factors into consideration there may be a place for more radical surgery in the patient older than forty years of age, not desiring fertility, presenting with recurrent endometriomas or imaging that reveals mural nodularity.(46)

5.2 Limitations:

A large number of the patients initially recruited into the study did not have 3 AMH values for comparison in the final analysis. This limitation is a result of the relatively high cost of the AHM assay in South Africa leading to many of the participants failing to repeat the investigations as requested. We do however include the long-term reproductive outcome of our cohort as a secondary outcome.

5.3 Conclusion:

The current available data does not report an initial negative effect on pregnancy rate after cystectomy for endometrioma. The long-term reproductive effect may however be dramatic. This is the first study to report on the long-term trend of serum AMH values following surgery for endometrioma and aims to address the paucity of data in this regard. With the negative impact on ovarian reserve due to traditional cystectomy for endometrioma now well proven, consideration of alternative surgical approaches such as hydro-dissection, the combined, 3-step technique or drainage alone in cases where fertility desire exist may be considered. One should be especially cautious in cases of bilateral or recurrent endometriomas, as the resultant loss of ovarian reserve after surgery could be dramatic. We again demonstrated the association of recto-vaginal endometriosis with endometrioma in more than half of patients. The potential finding of severe endometriosis should be anticipated when planning surgery in these cases and consideration given to the level of skill of the surgeon as well as involvement of a multi-disciplinary team and additional pre-operative assessment. Pre- and post-operative AMH determination should be done

and this information used in the counselling of patients to discuss the effects of surgery, fertility prognosis and alternative strategies such as oocyte vitrification.

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ADDENDUM

Table 1:

Characteristics of patients with endometrioma (n=50)		
	Mean(±SD)	n(%)
Age (y)	34.4(±6.07)	
BMI (kg/m^2)	25.3(±4.56)	
Previous Surgery		
Endometrioma		13(26)
Endometriosis		16(32)
Indication for Surgery		
Pain and Infertility		14(28)
Pain only		30(60)
Infertility only		6(12)
Concurrent Endometriosis		
Peritoneal		27(54)
Rectovaginal		27(54)
Endometrioma		
Unilateral		34(68)
Bilateral		16(32)

Table 2:

Mean AMH ng/ml(±SD) according to clinical findings.			
Endometrioma	Unilateral	Bilaterlal	*P* value
	(n=19)	(n=7)	
0 months	2.05±0.82	3.64±2.11	0.071
6 month	1.48±0.54	1.16±0.51	0.427
Final f/up	1.28±0.59	0.85±0.65	0.342
Endometriosis	Pertoneal	Rectovaginal	
	(n=11)	(n=16)	
0 months	3.60±0.81	2.29±0.97	
6 month	1.66±0.79	1.24±0.46	
Final f/up	1.17±0.95	1.19±0.59	

Table 3:

Reproductive Outcome	
	n(%)
Trying to conceive	34
Pregnancies	13(38)
Spontaneous	7(54)
Assisted	6(46)